Healthcare Improvement Scotland | SHTG Advice on health technologies

In response to enquiry from the Thrombectomy Advisory Group

Endovascular therapy using mechanical thrombectomy devices for treatment of patients with ischaemic stroke

Questions addressed

- Is mechanical thrombectomy, with or without intravenous thrombolysis, clinically effective compared with standard care for the treatment of ischaemic stroke? If so, does it remain clinically effective if intervention occurs more than 6 hours after symptom onset?

- Is mechanical thrombectomy, with or without intravenous thrombolysis, cost effective compared with standard care for the treatment of ischaemic stroke?

- What are the organisational issues associated with providing mechanical thrombectomy for patients with ischaemic stroke in Scotland?

What is an evidence note?

Evidence notes are rapid reviews of the evidence surrounding health technologies that are under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 2-3 month period and the final publication is usually complete within 6 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify, retrieve and develop within the time available.

The introduction and technology description from this extended evidence review are adapted from Evidence Note 61. The clinical and cost effectiveness sections have been updated with recent published evidence, however the focus of this evidence note is organisational issues associated with developing and delivering mechanical thrombectomy services for ischaemic stroke patients in Scotland. The scope of this evidence note was agreed with the Thrombectomy Advisory Group.

Key points

- A meta-analysis of eight RCTs (n=1,841) found that patients with ischaemic stroke treated with mechanical thrombectomy plus standard care were significantly more likely to be functionally independent at 90 days compared with patients treated with standard care alone: odds ratio (OR) 2.07, 95% confidence interval (CI) 1.70 to 2.51, p<0.00001. There were no statistically significant differences in 90-day mortality or symptomatic intracranial haemorrhage (ICH).

- In a meta-analysis of four RCTs (n=518), patients with ischaemic stroke treated with mechanical thrombectomy plus standard care a median of 10.8 hours after they were last known to be well, had significantly better odds of functional independence at 90 days compared with patients treated with standard care alone: OR 3.33, 95% CI 1.81 to 6.12, p<0.0001. Patients in two of the included RCTs had been selected using advanced imaging.

- A network meta-analysis found no statistically significant differences in functional independence at 90 days or symptomatic ICH in comparisons between mechanical thrombectomy devices (Trevo®, Solitaire™, aspiration) and between thrombectomy strategies (stent retriever or aspiration) for treatment of patients with ischaemic stroke.

- In a systematic review of eight economic evaluations mechanical thrombectomy using stent retriever devices was cost effective or dominant (less expensive and more effective) compared with standard medical care for treatment of ischaemic stroke.

- In a meta-analysis of eight studies (one RCT and seven retrospective cohorts, total n=2,068) the mean times from symptom onset to thrombolysis, puncture, and reperfusion for ischaemic stroke patients treated with mechanical thrombectomy were significantly shorter in a 'mothership' compared with a 'drip and ship' model of care. The mothership model was associated with a significantly higher rate of functional independence at 90 days compared with the drip and ship model: relative risk (RR) 0.87, 95% CI 0.77 to 0.98. There were no statistically significant differences in relative risk of 90-day mortality, symptomatic ICH or successful reperfusion.

- Two additional modelling studies reported differing conclusions on the most appropriate model of care (mothership or drip and ship) for organisation of mechanical thrombectomy services. Only one study accounted for the potential effects of an overwhelming volume of patients in mothership models and local skill reduction in drip and ship models.

- A retrospective study (118 hospitals, n=8,533) reported a statistically significant negative correlation between mechanical thrombectomy procedure volume and patient mortality rate: hospitals with higher procedure volume had significantly lower mortality (p=0.007).

- Two studies evaluating the learning curve for mechanical thrombectomy found no statistically significant differences in patient outcomes in comparisons of experienced and inexperienced clinicians.

- Introducing a mechanical thrombectomy service in Scotland has implications for NHSScotland including costs, staff resources, facility requirements (particularly imaging), ambulance service logistics and general infrastructure.

Contents

Literature search

A systematic literature search was carried out between 3 and 24 September 2018.

Secondary literature resources were searched to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline in process, Embase and the Cochrane Library databases were also searched for systematic reviews and meta-analyses.

A search of the primary literature (Medline, Embase and Cochrane Library) was carried out to identify RCTs, economic studies, volume-outcome and learning curve studies, and studies discussing models of service delivery.

All search results were limited to English language and 2014 onwards.

A Google search was used to identify reports on implementation or organisation of mechanical thrombectomy services.

Concepts used in searches included: thrombectomy, endovascular therapy, stent retriever, mechanical recanalisation and stroke. A full list of resources searched and terms used are available on request.

Introduction

A stroke occurs when a blood vessel that carries oxygen and nutrients to the brain is either ruptured or blocked by a thrombus (blood clot). Haemorrhagic stroke relates to the rupture of a weakened blood vessel. Ischaemic stroke results from an obstruction within a blood vessel supplying the brain and accounts for around 85% of all stroke cases[1].

The most common symptom of a stroke is sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include: confusion, difficulty speaking or understanding speech; difficulty seeing with one or both eyes; difficulty walking, dizziness, loss of balance or co-ordination; severe headache with no known cause; fainting or unconsciousness. The effects of a stroke depend on which part of the brain is injured and how severely it is affected. A very severe stroke can cause sudden death[2].

Stroke is a significant public health concern and the predominant cause of disability in adults in Scotland[3]. Stroke survivors may experience a range of significant physical, mental and emotional consequences[4].

Treatment for stroke depends on the results of brain imaging which differentiates haemorrhagic from ischaemic events and can exclude stroke mimics such as tumours. The primary treatment goal for ischaemic stroke is to restore blood flow to affected parts of the brain to improve functional outcomes for patients[5].

Health technology description

At least 15 CE-marked mechanical thrombectomy devices are available. Most are indicated for the restoration of blood flow in patients experiencing ischaemic stroke caused by a large intracranial vessel occlusion of the anterior circulation[4].

The aim of mechanical thrombectomy is to retrieve the thrombus and rapidly restore blood flow to the affected area. Devices may be broadly classified into one of three categories: coil retrievers (first-generation devices) with a mechanism akin to pulling a cork from a bottle, stent retrievers (second-generation devices) which work by enmeshing the clot inside a basket before removal, and aspiration/suction devices[4]. All require similar endovascular access and should be used as early as possible after stroke onset. In clinical trials, general anaesthesia was used in between 7% and 38% of procedures. Mechanical thrombectomy may be used in conjunction with intravenous and/or intra-arterial thrombolysis or as an alternative to it in patients experiencing an ischaemic stroke who are not candidates for thrombolysis or in whom thrombolysis appears to have failed.

Epidemiology

Stroke is the third commonest cause of death in Scotland and the most common cause of severe physical disability among Scottish adults[6]. In 2016–2017 there were 9,161 new cases of stroke in Scotland (new hospital admissions plus stroke deaths with no hospital admission)[7]. Approximately 87% of new stroke-related hospital admissions were for ischaemic stroke[6]. There were 4,153 deaths due to stroke in Scotland in 2016[7].

Over 75% of strokes occur in patients aged 65 or over; the mean age of stroke admissions in 2017 was 70 years for men and 76 years for women[6]. The European age-sex standardised incidence rate was 201 per 100,000 population for men and 160 per 100,000 population for women[7]. In the 2017 Scottish Health Survey, 3% of both men and women reported that they had experienced a stroke[8].

UK guidelines

The SIGN guideline on management of patients with stroke or transient ischaemic attack (TIA)[3] recommends that:

- "All patients with suspected stroke should have brain imaging immediately on presentation.
- Patients admitted with stroke within four and a half hours of definite onset of symptoms, who are considered suitable, should be treated with 0.9 mg/kg (up to maximum 90 mg) intravenous rt-PA *[recombinant tissue plasminogen activator, thrombolytic therapy]*.
- Mechanical thrombectomy using a stent retriever device should be considered for selected patients with ischaemic stroke who have confirmed large vessel occlusion:
  - o as an addition to standard treatment with thrombolytic drug therapy, or
  - o as an alternative to standard care for patients who are ineligible for thrombolytic drug therapy."

A recently published consultation on an update of the NICE guideline on stroke (Nov 2018) makes the following draft recommendations[9]:

- Offer thrombectomy within 6 hours of symptom onset, with intravenous (IV) thrombolysis, to people who have ischaemic stroke and confirmed occlusion of the proximal anterior circulation demonstrated by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA).

- Offer thrombectomy to people who were last known to be well between 6 hours and 24 hours previously who have ischaemic stroke (including wake-up strokes), confirmed occlusion of the proximal anterior circulation demonstrated by CTA or MRA and there is the potential to salvage brain tissue, as shown by CT or MRI scanning techniques.

- Consider thrombectomy alongside IV thrombolysis for people last known to be well up to 24 hours previously (including wake-up strokes) who have ischaemic stroke, confirmed occlusions of the proximal posterior circulation demonstrated by CTA or MRA and there is the potential to salvage brain tissue, as shown by CT or MRI scanning techniques.

- Take into account the following factors when considering thrombectomy (in addition to the recommendations above): pre-stroke functional status, clinical severity of stroke and extent of established infarction on initial brain imaging.

Clinical effectiveness

Evidence Note 61 (2016) reported the findings of a EUnetHTA meta-analysis on mechanical thrombectomy with/without IV thrombolysis compared with standard care, based on eight randomised controlled trials (RCTs) with a total of 2,423 patients[10]. All RCTs in the meta-analysis – MR RESCUE, IMS III, SYNTHESIS, MR CLEAN, EXTEND IA, REVASCAT, SWIFT PRIME, and ESCAPE – were published between 2005 and 2015. The meta-analysis concluded that mechanical thrombectomy using stent-based devices, as an addition to standard care, resulted in improved rates of functional independence at 90 days for selected patients with ischaemic stroke who have confirmed large vessel occlusion. There were no statistically significant differences in all-cause mortality at 90 days.

Three meta-analyses were identified that incorporated RCTs published after the EUnetHTA study[11-13]. Key characteristics of studies included in these meta-analyses are outlined in table 1. The RCTs in the meta-analyses recruited selected patients with large vessel occlusion of the anterior circulation confirmed by CTA or MRA, who could undergo thrombectomy within 5 hours (one study), 6 hours (six studies), 8 hours (one study) or 12 hours (one study) of symptom onset.

Table 1: characteristics of RCTs included in meta-analyses 2014–2018 on mechanical thrombectomy for treatment of patients with ischaemic stroke[9]

Study	N	Timing of thrombectomy	Imaging criteria	Patient selection criteria
THRACE (2016)	414	≤5 hours	Occlusion on CTA or MRA	Age 18-80; NIHSS 10-25; thrombolysis ≤4 hours
MR CLEAN (2015)	500	≤6 hours	Occlusion on CTA, MRA, or DSA	Age ≥18; NIHSS >2
EXTEND IA (2015)	70	≤6 hours	Occlusion on CTA or MRA; mismatch ratio >1.2; absolute mismatch volume >10ml; ischaemic volume <70ml	Thrombolysis ≤4.5 hours; age ≥18
SWIFT PRIME (2015)	196	≤6 hours	Occlusion on CTA or MRA	Age 18-80; pre-stroke mRS ≤1; NIHSS ≥8 and <30; thrombolysis ≤4.5 hours
THERAPY (2016)	108	≤6 hours	Occlusion on CTA	Age 18-85; eligible for thrombolysis; clot length >8mm; NIHSS >8
PISTE (2017)	65	≤6 hours	Occlusion on CTA or MRA	Age ≥18; thrombolysis ≤4.5 hours
REVASCAT (2015)	206	≤8 hours	Occlusion on CTA, MRA or angiography	Thrombolysis failed or contraindicated; age ≥18 and ≤80; NIHSS ≥6; pre-stroke mRS ≤1
ESCAPE (2015)	316	<12 hours	Occlusion on CTA	Age ≥18; NIHSS >5; pre-stroke modified Barthel Index >90
DEFUSE-3 (2018)	182	6-16 hours	Occlusion on CTA or MRA; infarct volume <70ml; ratio of ischaemic tissue volume to initial infarct volume ≥1.8; penumbra ≥15ml	Age 18-90; NIHSS ≥6; pre-stroke mRS 0-2
DAWN (2018)	206	6-24 hours	Occlusion on CTA or MRA; mismatch between severity and infarct volume assessed by diffusion weighted MRI or perfusion CT; <1/3 MCA involved on MRI or CT	Thrombolysis failed or contraindicated; age ≥18; NIHSS ≥10; pre-stroke mRS 0-1; life expectancy ≥6 months

CTA = computed tomography angiography; MRA = magnetic resonance angiography; NIHSS = National Institute for Health Stroke Score; DSA = digital subtraction angiography; mRS = modified Rankin Score; MCA = middle cerebral artery; MRI = magnetic resonance imaging; CT = computed tomography

The meta-analysis by Flynn *et al* (2017) compared mechanical thrombectomy using stent retriever or aspiration devices, with/without IV thrombolysis, with standard medical care for the treatment of ischaemic stroke[11]. The meta-analysis included an evaluation of the impact of three RCTs published since Evidence Note 61 (THERAPY 2016, THRACE 2016, PISTE 2017). Trial sequential analysis was used to determine whether sufficient RCTs have now been published to provide conclusive results for each outcome in the meta-analysis. A total of eight RCTs (n=1,841) were included in the meta-analysis: MR CLEAN, EXTEND IA, ESCAPE, REVASCAT, SWIFT PRIME, THERAPY, THRACE and PISTE. Seven of these trials stopped early due to pre-specified stopping points, loss of equipoise, or efficacy. All eight RCTs were judged to be at low overall risk of bias by the meta-analysis authors based on the Cochrane risk of bias tool.

Patients treated with mechanical thrombectomy plus standard care were significantly more likely to be functionally independent (modified Rankin Scale (mRS) 0 to 2) at 90 days: odds ratio (OR) 2.07, 95% confidence interval (CI) 1.70 to 2.51, eight studies, 1,841 patients, p<0.00001. There were no statistically significant differences in 90-day mortality or symptomatic intracranial haemorrhage (ICH) within seven days (table 2). Adding data from the three most recent RCTs did not alter the direction of effect or statistical significance of the results for any outcome reported in the meta-analysis (table 2).

Table 2: meta-analysis of RCTs comparing mechanical thrombectomy with/without thrombolysis with standard care and showing the effect of adding three recently published trials to five studies published in 2015[11]

Outcome	N studies (n patients)	Odds ratio (95% CI)	p value	I²
Functional independence (mRS 0-2) at 90 days	5 (1,278)	2.39 (1.88 to 3.04)	<0.00001	0%
	8 (1,841)	2.07 (1.70 to 2.51)	<0.00001	0%
90-day mortality	5 (1,282)	0.78 (0.54 to 1.12)	0.18	22%
	8 (1,841)	0.81 (0.61 to 1.07)	0.13	13%
Symptomatic ICH within seven days	5 (1,286)	1.06 (0.61 to 1.84)	0.84	8%
	7 (1,776)	1.21 (0.78 to 1.88)	0.40	0%

The trial sequential analysis concluded there was sufficient robust evidence of a benefit for mechanical thrombectomy compared with standard care for improved functional independence at 90 days in patients with ischaemic stroke. Results of the trial sequential analysis for 90-day mortality indicated a lack of robust evidence for a relative reduction in mortality that was unlikely to change with the addition of further RCTs. Well-designed observational studies may however provide additional information about long-term survival in patients undergoing mechanical thrombectomy.

Finally, the trial sequential analysis for symptomatic ICH within seven days indicated the meta-analysis was underpowered and that future RCTs may show a difference in this outcome. The meta-analysis authors noted that differing definitions of symptomatic ICH in the included studies and few recorded events may have influenced the results of the trial sequential analysis for this outcome.

The two other meta-analyses reached very similar conclusions, hence are not described further[12, 13].

Timing of mechanical thrombectomy

An individual patient data (IPD) meta-analysis, a meta-analysis of RCTs, and a draft NICE guideline each explored the effectiveness of mechanical thrombectomy for treating ischaemic stroke when intervention occurred after differing periods of time from symptom onset[9, 14, 15].

The IPD meta-analysis assessed the time from symptom onset in which mechanical thrombectomy was associated with clinical benefits and the extent to which treatment delay was related to patient outcomes[15]. Data were taken from five RCTs with 1,287 patients: MR CLEAN, ESCAPE, EXTEND IA, REVASCAT, and SWIFT PRIME. Participants in these trials were all treated within 6 hours, 8 hours (REVASCAT) or a maximum of 12 hours (ESCAPE) after symptom onset. Median time from symptom onset to randomisation into treatment groups was 196 minutes (3 hours 16 minutes) – this is considerably shorter than the median 10.8 hours reported in the meta-analysis of RCTs (see below). This difference in median time from symptom onset to randomisation is almost certainly explained by inclusion of the DAWN and DEFUSE-3 trials in the meta-analysis of RCTs, as the median time to randomisation was 10 hours and 12.5 hours in these two trials, respectively. Patients in all RCTs included in the IPD meta-analysis were selected based on CTA and/or MRA (table 1). The RCTs were judged by the IPD authors to be high quality using GRADE criteria. An independent statistician collated and checked the data from all the RCTs in preparation for the analysis.

In the IPD analysis the odds of functional independence at 90 days declined with increasing time from symptom onset to arterial puncture (table 3). Statistical significance for this outcome was first lost at 7 hours 18 minutes after symptom onset; there were too few patients treated after 8 hours to extend the time window further.

Table 3: odds of functional independence (mRS 0-2) at 90 days for ischaemic stroke patients treated with thrombectomy between 3 and 8 hours after symptom onset[15]

Time from symptom onset to arterial puncture	OR (95% CI)	Absolute risk difference
3 hours	2.83 (2.07 to 3.86)	23.9%
6 hours	2.32 (1.56 to 3.44)	18.1%
8 hours	2.03 (1.03 to 3.99)	14.3%

In the IPD meta-analysis, where patients received mechanical thrombectomy within a maximum of 8 hours from symptom onset, for every nine minute delay between symptom onset and substantial reperfusion, one in every 100 patients treated had a worse disability outcome (increased mRS score

of one or more levels). Similarly, for every four minute delay between arrival at hospital and reperfusion, one in every 100 patients treated with mechanical thrombectomy had a worse disability outcome. The frequency of functional independence at 90 days in patients receiving mechanical thrombectomy increased with faster emergency department to reperfusion times and brain imaging to reperfusion times. In patients who achieved successful reperfusion (n=1,000), every 15 minute reduction in emergency department to reperfusion time resulted in an estimated 39 patients having fewer disabilities at 90 days, including 25 additional patients achieving functional independence (mRS 0-2). There were no statistically significant differences in mortality rate or occurrence of symptomatic ICH in patients who achieved successful reperfusion with mechanical thrombectomy after longer time intervals from symptom onset up to a maximum of 8 hours.

The meta-analysis of RCTs contained four trials (ESCAPE, REVASCAT, DEFUSE-3 and DAWN) that compared mechanical thrombectomy, alone or in combination with thrombolytic therapy, with medical therapy alone for the treatment of ischaemic stroke due to occlusions in the anterior circulation[14]. Two studies (DEFUSE-3 and DAWN) were specifically investigating the effectiveness of mechanical thrombectomy at longer lengths of time since symptom onset: 6-16 hours in patients selected by perfusion imaging and 6-24 hours in patients with a mismatch between stroke severity and infarct volume, respectively. Unlike previous thrombectomy trials, participants in the DEFUSE-3 and DAWN trials were selected using advanced imaging, such as perfusion CT or diffusion-weighted MRI. Patients treated in the ESCAPE trial appear to have been selectively included in the meta-analysis if they were treated between 6 and 12 hours after symptom onset.

RCT participants (n=518) in the meta-analysis were treated a median of 10.8 hours after they were last known to be well (driven largely by the DAWN and DEFUSE-3 trials). Patients receiving mechanical thrombectomy more than 6 hours after they were last known to be well had significantly better odds of functional independence at 90 days (OR 3.33, 95% CI 1.81 to 6.12, p<0.0001, I^2=53%) and successful recanalisation (OR 13.17, 95% CI 4.17 to 41.60, p<0.0001, I^2=80%) compared with medical therapy alone. The analysis on successful recanalisation had high levels of between-study heterogeneity which was not explored by the authors other than conducting a random effects meta-analysis. There were no statistically significant differences in 90-day mortality or occurrence of symptomatic ICH. The authors of the analysis noted that RCTs with stricter imaging-based inclusion criteria showed greater benefits for mechanical thrombectomy and only 12% of patients in the RCT control groups received thrombolysis, both of which may have exaggerated the relative effectiveness of mechanical thrombectomy.

In the draft update of the NICE guideline on stroke the results from RCTs evaluating use of mechanical thrombectomy within 6 hours, 8 hours, 12 hours and 6-24 hours were pooled and reported separately (table 4)[9]. The difference in functional independence at 90 days remained statistically significant (and favoured thrombectomy over standard care alone) at all time periods assessed. In analysis of the RCT which reported outcomes for thrombectomy within 12 hours of symptom onset (ESCAPE), 90-day mortality was significantly lower in the thrombectomy group – this was the only analysis where there was a statistically significant difference in 90-day mortality. The difference in symptomatic ICH at 90 days was not statistically significant for any time period

analysed. The estimated absolute risk difference linked with the relative effects of thrombectomy compared with standard medical care alone are also provided in the draft NICE guidance (table 4).

Table 4: relative and absolute risk for clinical outcomes in RCTs of mechanical thrombectomy at different time periods after symptom onset[9]

Outcome	Studies	N patients	Relative risk (95% CI)	Estimated absolute risk difference (95% CI)
Thrombectomy ≤6 hours				
Functional independence (mRS 0-2) at 90 days	THRACE, MR CLEAN, EXTEND IA, SWIFT PRIME, THERAPY, PISTE	1,324	1.47 (1.28 to 1.68)	177 more per 1000 (6 to 256 more)
90-day mortality		1,334	0.9 (0.7 to 1.16)	16 fewer per 1000 (7 fewer to 25 more)
Symptomatic ICH at 90 days		1,312	0.98 (0.6 to 1.6)	1 fewer per 1000 (18 fewer to 26 more)
Thrombectomy ≤8 hours				
Functional independence (mRS 0-2) at 90 days	REVASCAT	206	1.55 (1.06 to 2.27)	155 more per 1000 (7 to 358 more)
90-day mortality			1.19 (0.65 to 2.18)	29 more per 1000 (54 fewer to 183 more)
Symptomatic ICH at 90 days			1.75 (0.53 to 5.8)	29 more per 1000 (18 fewer to 187 more)
Thrombectomy ≤12 hours				
Functional independence (mRS 0-2) at 90 days	ESCAPE	311	1.81 (1.36 to 2.42)	237 more per 1000 (105 to 416 more)
90-day mortality		311	0.54 (0.31 to 0.95)	88 fewer per 1000 (10 to 132 fewer)
Symptomatic ICH at 90 days		315	1.36 (0.39 to 4.74)	10 more per 1000 (6 fewer to 101 more)
Thrombectomy 6-24 hours				
Functional independence (mRS 0-2) at 90 days	DAWN, DEFUSE-3	388	3.16 (2.17 to 4.59)	322 more per 1000 (174 to 535 more)
90-day mortality			0.76 (0.41 to 1.40)	53 fewer per 1000 (129 fewer to 88 more)
Symptomatic ICH at 90 days			1.63 (0.66 to 4.06)	23 more per 1000 (13 fewer to 113 more)

Comparing thrombectomy devices

A Bayesian network meta-analysis (NMA) compared and ranked mechanical thrombectomy devices: two second-generation stent retriever devices (Trevo® and Solitaire™) and aspiration devices. The NMA also compared thrombectomy strategies (stent retriever versus aspiration) for the treatment of ischaemic stroke[16]. The NMA does not describe how the included RCTs were identified, nor does it report an assessment of the risk of bias for included studies. The analysis used Bayesian Markov chain Monte Carlo methods with 10,000 iterations to estimate the pooled effect. A fixed effect model was used as this had a better fit for the data in the Bayesian analysis than a random effects model. Thrombectomy devices and strategies were ranked using surface under the cumulative ranking curve (SUCRA) scores and rankograms based on the probability that each device or strategy was best for each positive outcome or best for preventing each negative outcome. No statistically significant heterogeneity or inconsistency was found in either the device or thrombectomy strategy network.

The network comparing devices for mechanical thrombectomy consisted of six RCTs with 871 patients (SWIFT, TREVO-2, EXTEND-IA, SWIFT-PRIME, REVASCAT, THERAPY). In each RCT a specific thrombectomy device had been used in more than 85% of trial participants allocated to the mechanical thrombectomy group. More than 50% of patients in the network (n=472) were treated using the Solitaire™ stent retriever device. The first-generation Merci® thrombectomy device was included in the network to connect the Trevo® stent retriever to other devices in the network. There were no statistically significant differences in functional independence at 90 days for comparisons between the Trevo® stent retriever, Solitaire™ stent retriever and aspiration thrombectomy devices (table 5). Both the Trevo® and Solitaire™ stent retriever devices were associated with significantly higher odds of functional independence at 90 days compared with standard medical care. There were no statistically significant differences in symptomatic ICH rate between Trevo®, Solitaire™ and aspiration thrombectomy devices. The Trevo® stent retriever device had the highest probability (92%) of being best for functional independence at 90 days.

Table 5: functional independence at 90 days (mRS 0-2) in a network meta-analysis comparing mechanical thrombectomy devices in patients with ischaemic stroke[16]

Trevo®				
1.63 (0.57 to 4.37)	Solitaire™			
2.41 (0.62 to 9.41)	1.51 (0.62 to 3.87)	Aspiration		
2.43 (1.26 to 4.69)	1.53 (0.73 to 3.30)	1.01 (0.31 to 3.16)	Merci®	
4.14 (1.41 to 11.80)	**2.55 (1.75 to 3.74)**	1.68 (0.72 to 3.87)	1.67 (0.69 to 3.79)	Medical

The network for comparing thrombectomy strategies (stent retriever versus aspiration) consisted of seven RCTs with 1,737 patients: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT, THERAPY, ASTER. In all RCTs the participants randomised to mechanical thrombectomy were treated with the same thrombectomy strategy – stent retriever or aspiration. The majority of patients in the network (n=1,278) were treated with a stent retriever strategy. There were no statistically significant differences in functional independence at 90 days or symptomatic ICH in the network meta-analysis comparing stent-retriever and aspiration thrombectomy strategies. Both stent retriever and aspiration thrombectomy strategies resulted in a significantly greater probabilities of 90 day functional independence compared with standard medical care: OR 2.38, 95% CrI 1.89 to 2.98 and OR 1.92, 95% CrI 1.24 to 2.86, respectively.

The NMA authors concluded that the Solitaire™ stent-retriever, Trevo® stent-retriever and aspiration thrombectomy devices all potentially had a time and place for use as first-line treatment for patients with ischaemic stroke.

Safety

Safety outcomes for mechanical thrombectomy reported in the secondary literature – mortality and symptomatic ICH – have been discussed in the clinical effectiveness section. Additional safety issues can arise due to device-related vascular injury, vascular access complications or use of radiological contrast media[5]. No new evidence on these outcomes was identified for this update.

Cost effectiveness

A systematic review of economic evaluations on stent retriever thrombectomy for ischaemic stroke due to large vessel occlusion identified eight relevant studies from North America and Europe, two of which were conducted in the UK[17]. A healthcare system perspective and lifetime horizon were adopted in most studies, including the UK-based ones. Overall, studies were rated good quality (mean score 79%, range 70% to 90%) by the systematic review authors based on quality assessment using the consolidated health economic evaluation reporting standards (CHEERS) and Phillips checklists. Data sources, effectiveness outcomes and other input parameters were heterogeneous across studies, however the studies reached similar conclusions on cost effectiveness of stent retriever thrombectomy for ischaemic stroke. In three studies stent retriever thrombectomy was less expensive and more effective (the 'dominant' strategy) compared with standard medical care alone. In five studies stent retriever thrombectomy was more expensive and generated more quality-adjusted life years (QALYs) but had a high probability (79% to 100%) of being cost-effective at conventional thresholds.

There are two published studies, and one study pending publication, that were conducted in the UK and are therefore directly applicable to Scotland[9, 18, 19]. One of the UK-based studies was included in the systematic review of economic evaluations and described in Evidence Note 61[10, 19]. This cost-

utility study demonstrated that, compared with thrombolysis alone, mechanical thrombectomy in addition to thrombolysis is a cost effective option with an incremental cost effectiveness ratio (ICER) of £7,061 per quality adjusted life year (QALY).

The second published UK-based study was included in the systematic review of economic evaluations but not described in Evidence Note 61. Detailed results were extracted from this study as it is directly applicable to Scotland[18]. The study assessed the cost effectiveness of stent retriever thrombectomy using the Solitaire™ device plus IV thrombolysis compared with standard medical care. The analysis took a UK healthcare provider perspective, used data from the SWIFT-PRIME RCT and had a lifetime time horizon. The quality assessment for this study reported in the systematic review of economic evaluations by Boudour *et al* (2018) was 89%[17]. Stent retriever thrombectomy with the Solitaire™ device resulted in greater health gains (2.31 additional QALYs) and lower costs (£33,190 cost saving per patient) compared with standard medical care, and was hence the dominant strategy. The net monetary benefit per patient was £79,390. Both the average cost per mRS score avoided at 90 days and the cost per additional functionally independent patient at 90 days were cost saving (-£33,486 and -£132,064, respectively). In probabilistic sensitivity analyses stent retriever thrombectomy plus IV thrombolysis had a 98.6% likelihood of being cost effective compared with standard medical care at a threshold of £20,000 per QALY.

The unpublished UK-based study was reported in the NICE draft guideline and evaluates cost effectiveness of thrombectomy compared with standard medical care at longer time intervals from symptom onset based on the DAWN and DEFUSE-3 trials[9]. At 12, 18 and 24 hours after symptom onset thrombectomy remained a cost effective option with an ICER below £5,000 per QALY.

Service delivery models

'Mothership' versus 'drip and ship'

Due to the equipment and expertise required to perform mechanical thrombectomy most procedures occur at a small number of specialist centres with on-site neuroendovascular capabilities[20]. However, many stroke patients are initially taken to the nearest hospital, which may not offer thrombectomy, to ensure rapid access to thrombolysis. Two models for delivering stroke care that includes mechanical thrombectomy have therefore been proposed: the 'mothership' and 'drip and ship' models. In the mothership model, all suspected ischaemic stroke patients are transported directly to a hospital offering mechanical thrombectomy, even if this is not the closest hospital. With the drip and ship model, patients are taken to the nearest hospital for thrombolysis therapy and initial imaging, then transferred to a hospital offering thrombectomy if appropriate. The choice between mothership and drip and ship models of service delivery may depend on multiple factors such as geography, travel times, availability of experienced staff, the urban-rural split, and volume of stroke patient admissions per annum[21].

A systematic review with meta-analysis and two primary modelling studies – published after the review inclusion period – compared the mothership model with a drip and ship approach[20-22]. The systematic review with meta-analysis compared the two approaches for treatment of patients with

ischaemic stroke due to large vessel occlusion in the anterior circulation (n=2,068)[20]. Eight studies were included in the review: one small RCT and seven retrospective analyses of database cohorts. One study was unpublished and had been submitted for publication by the systematic review authors. As the majority of studies were non-randomised, study participants were treated at the nearest hospital regardless of whether the hospital offered mechanical thrombectomy. All included studies were judged to be good quality by the systematic review authors using the Newcastle Ottawa Scale. The review authors only reported clinical and procedure outcomes. Mean time from symptom onset to thrombolysis, symptom onset to puncture and symptom onset to reperfusion, were all significantly shorter for patients treated under the mothership model compared with the drip and ship approach (table 6).

Table 6: mean difference in time from symptom onset under the mothership model compared with the drip and ship approach in a meta-analysis of eight studies[20]

	Mean reduction in time mothership vs drip and ship (95% CI)
Symptom onset to thrombolysis (min)	-16.85 (-21.83 to -11.86)
Symptom onset to puncture (min)	-83.05 (-89.09 to -77.01)
Symptom onset to successful reperfusion (min)	-94.33 (-100.42 to -88.24)

In both the adjusted and unadjusted meta-analysis the mothership model was associated with a significantly higher rate of functional independence at 90 days compared with the drip and ship model (table 7). There were no statistically significant differences in relative risk of 90 day mortality, symptomatic ICH or successful reperfusion.

Table 7: outcomes for patients treated under the mothership model compared with the drip and ship approach (adjusted and unadjusted meta-analysis)[20]

Outcome	Adjusted relative risk (95% CI)	Unadjusted relative risk (95% CI)
Functional independence at 90 days (mRS ≤ 2)	0.87 (0.77 to 0.98)	0.87 (0.81 to 0.93)
90 day mortality	1.21 (0.89 to 1.64)	1.00 (0.84 to 1.19)
Symptomatic ICH	1.53 (0.79 to 2.98)	1.37 (0.91 to 2.06)
Successful reperfusion	1.00 (0.92 to 1.10)	1.05 (0.95 to 1.15)

One modelling study published after the systematic review, explored options for national stroke and thrombectomy service organisation in NHS England[21]. The study used a genetic algorithm and data from 238,887 ischaemic and haemorrhagic stroke patient admissions in England 2013–2015.

Algorithm parameters were given pre-specified limits: hospitals providing mechanical thrombectomy had to perform a minimum of 150 procedures per year to maintain clinician competence; centres offering thrombectomy needed a minimum of 1,500 stroke admissions per year and units not offering thrombectomy required a minimum of 600 stroke admissions per year; each unit had a maximum sustainable number of stroke admissions of 2,000 per year; a 60 minute net delay in addition to transport to a thrombectomy hospital was assumed in the drip and ship model. An 'allowable delay' of 15 minutes was added to one analysis to emulate ambulance services transporting some patients directly to a more distant thrombectomy centre. Limitations of the analysis include necessary simplification of real-world stroke care, the assumption that all hospitals provide treatment at equivalent speeds and not accounting for increasing stroke incidence in an aging population.

The number of thrombectomy centres required for the mothership model was highly sensitive to changes in the proportion of eligible patients and the minimum required volume of thrombectomies per centre per year[21]. If the mothership model was applied to the 24 existing comprehensive stroke centres offering thrombectomy in NHS England, the average patient travel time was 38 minutes and annual stroke admissions at individual centres ranged from 1,264 to 6,117 per annum. In all scenarios involving the 24 existing thrombectomy centres and a mothership model, the upper limit of desirable admissions volume (2,000 per annum) was substantially exceeded for many centres, indicating overloading of individual centres' capacity. To maintain the estimated 1,500 thrombectomy procedures per year required to maintain competence, hospitals offering this treatment under a mothership model would require 2,750–3,000 stroke admissions per year which is beyond current capacity estimates based on the largest English thrombectomy centres.

To evaluate the drip and ship model the 24 current thrombectomy centres were included and each of the 103 hyper-acute stroke units (that provide thrombolysis but not thrombectomy) were sequentially added to the algorithm[21]. Increasing the number of hyper-acute units in the model reduced the average time to thrombolysis but increased the average time to thrombectomy. If all 103 existing hyper-acute units were included in the algorithm the average time to thrombolysis was reduced from 38 minutes to 18 minutes and the average time to thrombectomy increased from 30 minutes to 96 minutes. All solutions for the drip and ship model that maintained target annual admissions of 600–2,000 patients per centre per annum required 57 to 82 stroke centres in total, with the 24 existing thrombectomy centres continuing to provide this treatment. Analyses that allowed for a maximum delay of 15 minutes caused by transferring 25% of patients directly to a thrombectomy centre reported the average time to thrombolysis increased by 8 minutes and the average time to thrombectomy was reduced by 80 minutes. As the duration of allowable delay increased, direct admissions to thrombectomy centres increased while admissions to hyper-acute units decreased which would have implications for both types of unit in terms of capacity and competency.

The study authors concluded that an overall drip and ship model, with a mix of hospitals offering mechanical thrombectomy and hyper-acute units offering thrombolysis, had the highest probability of being suitable for NHS England. In dense population areas, such as London, the mothership model may be more appropriate as fewer patients would live long distances from a hospital offering

mechanical thrombectomy. More hyper-acute units are likely to be needed in rural and less densely populated areas to facilitate timely transfer of patients and access to thrombolysis. The study authors noted that the ideal service model for an individual patient may not be the best option for the overall stroke population/service.

The second modelling study calculated the probability of achieving a good clinical outcome for suspected ischaemic stroke patients transported to hospital under the mothership or drip and ship model in the Republic of Ireland[22]. The study authors applied both real and optimised transport and treatment time data from the Irish healthcare system. The analysis assumed ischaemic stroke could be accurately identified by emergency service staff and only considered ground transport of patients for both models. The analysis made no allowance for admission volume capacity at the thrombectomy centre or for maintaining skills at hospitals not offering thrombectomy.

From the Irish National Stroke Register, 699 ischaemic stroke patients were identified: 312 patients had received mechanical thrombectomy, 258 under the drip and ship model. Based on real data and the assumption that only one specialist centre was providing mechanical thrombectomy, the two models of service delivery were equivalent for most postcode-defined regions of the Republic of Ireland. When a second thrombectomy centre was added the mothership model became the better option for most regions. The best model for service delivery was very dependent on treatment times: the drip and ship model was the most beneficial if the time from hospital arrival to thrombolysis was reduced to 30 minutes or when all time periods (hospital arrival to thrombolysis, hospital arrival to puncture, in-hospital turnaround time) were optimised. Time from hospital arrival to reperfusion was much quicker for the drip and ship model: median 10 minutes compared with median 110 minutes. This is probably because the thrombectomy centre could be notified when a patient was being transferred so they could prepare for the procedure. If the turnaround time at the initial hospital remains long the drip and ship model is rarely better than the mothership approach. The mothership model did however prevail in areas close to hospitals offering mechanical thrombectomy.

Adapted service delivery models

Two studies described adaptations of the drip and ship model of service delivery in which the interventional radiologist or an interventional stroke team travel to the hospital where a stroke patient has been admitted and perform the mechanical thrombectomy locally rather than having the patient transferred to a hospital offering thrombectomy[23, 24]. The proposed advantage of the adapted model in both studies was the ability to 'parallel process' whereby patients are prepared for mechanical thrombectomy while the clinical specialists are in transit.

The first study was a prospective analysis of 74 consecutive ischaemic stroke patients admitted to three hospitals in Germany: one comprehensive stroke centre offering thrombectomy and two local stroke units[23]. The two local stroke units were 53km and 63km from the comprehensive stroke centre. The drip and ship model was compared with what the authors described as a 'drip and drive' model. In the latter an interventional neuroradiologist travels from the comprehensive stroke centre to the local stroke unit when a suitable patient has been admitted. The results of this study may be

affected by bias due to differences in the hours of thrombectomy availability at the comprehensive stroke centre (24/7) and local hospitals (working hours only). Forty-two patients were treated under the drip and drive model and 32 with the drip and ship approach. Median time for neuroradiologist travel was 60 minutes less than the median patient transfer time: 121 minutes (inter-quartile range (IQR) 108 minutes to 134 minutes) compared with 181 minutes (IQR 157 minutes to 219 minutes), p<0.001. Median time from symptom onset to recanalisation was significantly shorter with the drip and drive model compared with the drip and ship model: 270 minutes (IQR 249 minutes to 319 minutes) versus 387 minutes (IQR 368 minutes to 416 minutes), p=0.001. Selected time intervals measured in this study are reported in table 8.

Table 8: selected time intervals for the drip and drive versus drip and ship model of mechanical thrombectomy service delivery[23]

Time interval	Drip and drive			Drip and ship			p value
	N	Median (min)	IQR (min)	N	Median (min)	IQR (min)	
Symptom onset to CT scan	31	88	59 to 124	23	84	67 to 100	0.896
Symptom onset to angiography	30	201	176 to 242	15	349	319 to 384	<0.001
Symptom onset to recanalisation	22	270	249 to 319	11	387	368 to 416	0.001
CT scan to angiography	41	123	93 to 147	23	252	228 to 275	<0.001
CT scan to call neuroradiologist	40	37	24 to 54	22	40	29 to 54	0.541

The second study compared the drip and ship model with a 'trip and treat' model where a mobile interventional stroke team from a comprehensive stroke centre travelled to one of three local hospitals with interventional capacity in Manhattan (New York) when suitable patients were admitted[24]. Data from 87 consecutive patients were retrospectively analysed: 39 patients treated using the trip and treat model and 47 under the drip and ship model. Patients were excluded from the study if they presented at a hospital more than 20 miles from the comprehensive stroke centre. The model a patient was treated under was determined by the availability of operating theatres and neurosurgical intensive care unit (ICU) beds at the admitting hospital and thrombectomy centre, which may have biased the study results. There was no statistically significant difference in mean travel time for the interventional team in the trip and treat model compared with mean patient transfer time in the drip and ship group. The time from initial arrival at the first hospital to puncture was 79 minutes shorter in the trip and treat group: 143 minutes (standard deviation (SD) 41 minutes) versus 222 minutes (SD 55 minutes), p<0.0001. The time from initial arrival at hospital to

recanalisation was 68 minutes shorter in the trip and treat group: 199 minutes (SD 53 minutes) versus 267 minutes (SD 56 minutes), p<0.0001.

Service delivery: consensus in NHS England

Between November 2015 and January 2017 a Delphi survey and ranking exercise were conducted among clinicians in NHS England to establish consensus on options for future organisation of national mechanical thrombectomy services[25]. In the Delphi study, twelve options for organising mechanical thrombectomy services for ischaemic stroke were presented to a purposive sample of clinicians who were members of the British Association of Stroke Physicians (BASP) and had experience in managing large artery occlusive stroke. A maximum of three Delphi rounds were planned with propositions falling into the lowest quartile of votes at the end of each round being discarded. Approval was defined as ≥75% of respondent ratings falling into three categories on a seven-point Likert scale: approve, quite strongly approve or very strongly approve. Options that gained approval in the Delphi study were then ranked by consultation with a larger sample of clinicians drawn from all members of BASP and the British Society of Neuroradiologists (BSNR).

Fifteen panelists from all regions of England contributed to the first Delphi round and eleven subsequently responded in the second round. Approval was reached for three options:

- "Local CT/CTA *[computed tomography/computed tomography angiography]* then transfer all large artery occlusive stroke patients to nearest neuroscience centre for interventional neuroradiologist delivered 'expert thrombectomy'" (91% approval)

- "Local CT/CTA then transfer large artery occlusive stroke patients to nearest neuroscience centre for advanced imaging and 'expert thrombectomy'" (82% approval)

- "Selective transfer to nearest on-call neuroscience centre for 'expert thrombectomy'" (100% approval)

Responses to the ranking exercise for these three options were received from 43 BASP members and 21 BSNR member (representing 15% of the membership of each). Clear consensus was reached in the ranking exercise for the simple imaging-driven drip and ship model of service organisation: "patients with large artery occlusive stroke are transferred to nearest *[neuroscience]* centre for thrombectomy based on local CT/CT angiography alone" (97% BASP and 86% BSNR respondents).

Thrombectomy services: international case studies

Experiences and assessments were sought from countries in Europe and North America where mechanical thrombectomy services for ischaemic stroke have already been implemented.

Thrombectomy in the UK

Most stroke patients in Scotland are currently managed in integrated stroke units as there are no comprehensive stroke centres. Up until summer 2018, the Western General Hospital in Edinburgh was conducting a small number of thrombectomy procedures in patients with ischaemic stroke (13

in 2017)[6]. This is the only facility in Scotland to have offered mechanical thrombectomy for ischaemic stroke patients.

In March 2018 NHS England approved commissioning of mechanical thrombectomy services for ischaemic stroke patients meeting the following strict criteria[26]:

- Thrombectomy can be achieved within 6 hours of symptom onset OR advanced brain imaging indicates substantial salvageable brain tissue at up to 12 hours after symptom onset AND

- There is inadequate response to thrombolysis OR the patient cannot have thrombolysis AND

- Proximal occlusion of the anterior cerebral circulation is demonstrated on vascular imaging AND

- There are no new ischaemic changes on CT or MRI scans AND

- There is significant new disability (National Institute for Health stroke score (NIHSS) >5) AND

- The patient was previously independent (mRS <3).

If all these criteria are met the patient is eligible for mechanical thrombectomy under a drip and ship model of service delivery. There are currently 24 NHS England facilities performing mechanical thrombectomy; almost exclusively regional neuroscience centres with neurointerventionists[25, 27].

Between April 2016 and March 2017 mechanical thrombectomy was used in a total of 537 patients in England, Wales and Northern Ireland[27]. There is however continued variation in the volume of thrombectomy procedures and provision of stroke care across England due to financial and workforce constraints.

In Northern Ireland thrombectomy is only available within working hours at a single hospital in Belfast[27]. In 2015 the Northern Ireland Stroke Network developed regional referral guidelines to support coordination of thrombectomy services[27]. Key aspects of this guidance include:

- Involvement of all trusts and ambulance services
- A comprehensive care pathway including transport to hospital and repatriation after thrombectomy
- Agreement that imaging will be provided at the initial admitting hospital
- Clear communication and advance alerts regarding potential patients for neuroradiologists and hospitals providing thrombectomy
- Stroke and neuroradiology teams working together to ensure rapid imaging and intervention.

Republic of Ireland

There is one centre that provides mechanical thrombectomy in the Republic of Ireland (it is unclear if there is 24/7 access)[22]. A second thrombectomy centre is currently in development.

The Health Information and Quality Authority (HIQA) recommended that provision of mechanical thrombectomy in the Republic of Ireland be confined to a small number of comprehensive stroke centres with access to neurosurgical care, advanced brain imaging and neuroendovascular expertise[28]. Key organisational factors identified by HIQA include timely presentation of patients at hospital, prompt access to diagnostic imaging, access to specialist stroke care and formalised protocols for rapid transfer of patients to comprehensive stroke centres with thrombectomy capability. Taking these factors in order, HIQA:

- Proposed an additional stroke public awareness campaign

- Identified the need for a second dedicated biplane angiography suite to facilitate rapid imaging without delaying emergency or elective procedures for other patients

- Noted that attempting to provide thrombectomy services at all stroke units would not be feasible as there would be insufficient patient volume to maintain clinical competence

- Acknowledged the potential economic and opportunity costs for ambulance services due to prolonged transport times for patients travelling to comprehensive stroke centres or between hospitals.

HIQA therefore suggest a 'hub and spoke' approach to thrombectomy service delivery which is a variant on the drip and ship model discussed earlier.

Norway

The Norwegian Institute for Public Health produced a health technology assessment (HTA) that included a chapter on organisation of national mechanical thrombectomy services[29, 30]. This chapter was based on input from a group of experts, reports from international HTA organisations and data from Norwegian healthcare bodies. Issues addressed include facility requirements, staff and equipment needs, and logistics of national service organisation. With the help of the expert group the stroke care pathway was mapped and data collected on the number of primary stroke care units and stroke intervention centres. Issues relating to demographics, geography and climate were identified as potentially impacting on delivery of a national thrombectomy service. A key challenge was the conflict between the need for decentralised thrombolysis to facilitate early intervention and the need for centralisation of specialist stroke services such as thrombectomy. Other factors considered in the Norwegian assessment include:

- Co-ordination between services (ambulance and hospital) and hospital departments

- Training for ambulance services on triage of patients with suspected stroke

- Time constraints on the efficacy of thrombectomy, requiring speedy transfer of patients to hospital and rapid access to neuroimaging

- Clinical competence and experience of thrombectomy procedures need to be developed and maintained.

Two new intervention centres have been created in Norway to provide mechanical thrombectomy on a drip and ship basis.

Austria

An Austrian HTA agency explored criteria used to select patients suitable for mechanical thrombectomy in RCTs, clinical guidelines and expert opinion[31]:

- Age
- Functional ability prior to stroke onset (measured using the mRS or Barthel Index)
- Clinical diagnosis (NIHSS)
- Time to treatment initiation
- Anatomy of affected vessel
- Location of intracranial occlusion.

Based on these criteria it was estimated that 19% of ischaemic stroke patients in Austria would be suitable for mechanical thrombectomy.

A recent update from the European Stroke Network indicated there are now ten centres providing mechanical thrombectomy for ischaemic stroke patients in Austria[32]. An evaluation by the Network identified two sources of delay in thrombectomy treatment: in-hospital delays associated with imaging (particularly if radiology was distant from the stroke treatment location) and type of transport used to deliver patients to hospital (helicopter, ambulance, ambulance with on-board emergency physician).

France

In France clinical experts and stakeholders were consulted on organisational requirements for a national neurovascular care pathway that included mechanical thrombectomy[33]. Difficulties were encountered in these consultations due to lack of consensus. The evaluation concluded there was no single nationwide solution to provision of thrombectomy services in France. A substantial increase in mechanical thrombectomy procedures of approximately 30% since 2015 led to the need for an estimated ten additional senior doctors (there are currently 109) trained to perform thrombectomy by 2020.

Slovakia

In Slovakia there are five hospitals providing mechanical thrombectomy, compared with 40 hospitals delivering thrombolysis, for stroke patients[32]. Improvements to stroke care in Slovakia have focused on shortening the care pathway and implementing better communication strategies. Innovations include requiring the on-duty neurologist at each thrombectomy-capable hospital to carry a stroke-dedicated mobile phone to receive calls from ambulance crews in the field; a nationwide android application that alerts the on-duty neurologist that a stroke patient has been seen by an ambulance crew; and pre-notification of the receiving hospital that a stroke patient is en-route. Whilst the ambulance crew is en-route to the hospital, the neurologist arranges a CT scan to determine if the

patient is suitable for thrombectomy and the patient is initially taken directly to neuroimaging rather than the emergency department.

British Colombia (Canada)

The University of Calgary in British Colombia developed four scenarios for implementation of thrombectomy services in the province[34]. These scenarios were based on the assumption that time from arrival at hospital to initial CT scan was 30 minutes and time from arrival at hospital to groin puncture was ≤30 minutes. The scenarios offered a 'no adoption' option, an expansive adoption model, and two incremental strategies. The drip and ship model of care was used in all scenarios, with only patients living close to a thrombectomy centre being directly admitted.

The four scenarios considered were:

- No support for mechanical thrombectomy: all hospitals currently performing thrombectomy cease to offer this treatment.

- "As is" with no transport coordination: three current thrombectomy centres continue to provide thrombectomy and no changes are made to patient transport arrangements.

- Increased catchment area and coordinated transport: three hospitals provide thrombectomy to larger catchment areas, facilitated by formalised coordination of patient transport.

- Expansive adoption: the number of hospitals providing thrombectomy is increased to four and all operate with increased catchment areas facilitated by coordinated patient transport.

Unfortunately it has not been possible to determine which scenario has been implemented in British Colombia.

Volume-outcome

A retrospective study compared mortality rates for ischaemic stroke patients treated with mechanical thrombectomy at low, medium and high volume hospitals, and compared mortality rates for patients directly admitted to a hospital with mortality rates in patients transferred to a higher volume centre[35]. Data from 118 hospitals (n=8,533 patients) were extracted from a database voluntarily populated by participating institutions between October 2012 and June 2016. The non-mandatory nature of the database and the use of a time period where evidence on mechanical thrombectomy was evolving may have introduced bias to this study. No data on patient functional outcomes or severity of stroke were recorded in the database. Low volume hospitals were defined as those performing less than 27 thrombectomy procedures during the study period (3.75 years), medium volume hospitals ≥27 to <132 thrombectomy procedures, and high volume hospitals ≥132 thrombectomy procedures.

There was a statistically significant negative correlation between hospital thrombectomy procedure volume and patient mortality rate (r^2=0.06, p=0.007). Mortality rates were significantly higher in low volume hospitals compared with medium volume hospitals (19.7% versus 14.9%, p=0.01) and high volume hospitals (19.7% versus 9.8%, p=0.001). There were no statistically significant differences in

mortality rates between medium and high volume hospitals. Mortality rates for patients directly admitted for thrombectomy at a low volume hospital were significantly higher than for patients directly admitted to medium volume hospitals (20.4% versus 14.2%, p=0.007) and patients transferred to a high volume centre (20.4% versus 10.0%, p=0.005). There were no statistically significant differences in mortality rates following thrombectomy between direct admissions to low volume hospitals and patients transferred to a medium volume hospital. Mortality rates were significantly higher in patients directly admitted to a medium volume hospital for thrombectomy compared with patients transferred to a high volume hospital (14.2% versus 10.0%, p=0.042). These results suggest that the benefits of being treated with mechanical thrombectomy at a high volume hospital may outweigh any detrimental effects of transferring patients between facilities.

Learning curve

Two studies evaluated the learning curve for clinicians performing mechanical thrombectomy based on data recorded prior to initiation of multicentre RCTs[36, 37]. The first, a retrospective study, explored the effect of interventionists' experience on procedural, clinical and patient outcomes following mechanical thrombectomy[37]. Data were extracted from the pretrial registry for the MR CLEAN trial and were available for 80 interventionists with prior experience of performing endovascular procedures. Experience was categorised as low (0–5 procedures), minimal (6–15 procedures) and moderate (>16 procedures). The median number of procedures by an interventionist was 11 (range 1 to 49) therefore results may not generalise to clinicians with more extensive experience. In an adjusted regression analysis of 313 highly selected patients there were no statistically significant associations between interventionist experience level and recanalisation rates, neurological outcomes, functional outcomes, adverse events or duration of procedure. When the analysis was repeated using 350 patients selected using less strict criteria there were no statistically significant differences in recanalisation rates, neurological outcomes, functional outcomes or adverse events. Procedure time was significantly shorter for more experienced interventionists.

The second study compared outcomes for ischaemic stroke patients treated with the Solitaire™ stent retriever device during the roll-in phase of the SWIFT trial with outcomes in patients receiving Solitaire™ stent retriever thrombectomy during the randomised phase of the trial[36]. The US-based clinicians in this study had no prior experience with the Solitaire™ stent retriever device but did have experience of mechanical thrombectomy using the first-generation Merci® stent retriever device. The neurointerventionists also received training on the Solitaire™ device using a bench vascular model prior to performing any procedures in patients. Thirty-one patients were treated with the Solitaire device during the roll-in phase and 58 during the randomised phase of the SWIFT trial. No statistically significant differences in neurological outcomes, mortality at 90 days or serious adverse events were reported for patients treated using Solitaire™ stent retriever thrombectomy during the roll-in compared with the randomised phase of the SWIFT trial.

Resources and infrastructure

Patient selection criteria

Criteria for selecting ischaemic stroke patients who may be suitable for mechanical thrombectomy have been proposed in international guidelines, English commissioning guidance and RCTs (table 9)[26, 31, 38, 39]. The majority of sources clearly state that patients must meet all of the criteria listed in table 9 in order to be eligible for mechanical thrombectomy. Additional criteria proposed for patient selection include:

- Advanced brain imaging indicating substantial salvageable brain tissue at ≤12 hours after symptom onset (as an alternative to thrombectomy achieved ≤6 hours)[26]

- Patient has inadequate response to IV thrombolysis administered within 4.5 hours of symptom onset or cannot have IV thrombolysis[26]

- No new ischaemic changes are evident on CT or MRI scans[26].

Table 9: proposed criteria for selecting ischaemic stroke patients for mechanical thrombectomy

Criterion	European Stroke Organisation[39]	American Stroke Association[38]	NHS England[26]	RCT entry criteria[31]
Time from symptom onset	≤6 hours	≤6 hours	≤6 hours	<11 hours*
Age	All ages	≥18 years	All ages	≥18 years
NIHSS	≥7	≥6	>5	≥2
ASPECTS	–	≥6	–	≥6
Location	Large vessel occlusion	Occlusion of internal carotid artery or MCA1	Proximal occlusion of anterior circulation	Anterior circulation occlusion
mRS score	–	≤1	<3	≤1

*symptom onset to door time.
ASPECTS = Alberta Stroke Programme Early CT score. MCA = middle cerebral artery.

Thrombectomy provision and population size

A recent study developed a decision-tree model based on data from international RCTs and national registries to estimate the number of ischaemic stroke patients eligible for mechanical thrombectomy each year in the UK[40]. Patients were excluded from the eligible population based on criteria such as small artery occlusion rather than large artery occlusion, mild stroke, presentation more than 12 hours after symptom onset, and results from advanced imaging. The authors estimated that between 9,620 and 10,920 ischaemic stroke patients would be eligible for mechanical thrombectomy in the UK each year – approximately 10% of stroke admissions. Applying the decision-

tree model in this study to data from ISD Scotland, approximately 936 to 1,012 ischaemic stroke patients in Scotland would be eligible for mechanical thrombectomy each year[7].

Data in table 10 illustrate the number of stroke centres relative to the total population and stroke population in countries described in case studies in this Evidence Note.

Table 10: number of thrombectomy centres relative to population size in selected countries

Country/Region	Population (million)	Estimated strokes per annum	N thrombectomy centres
Northern Ireland	1.87	3,784	1
Republic of Ireland	4.78	10,000	1–2
British Colombia (Canada)	4.82	6,500	3-4
Norway	5.31	11,000	5
Scotland	5.42	9,161	0
Slovakia	5.44	9,491	5
Austria	8.84	25,000	10
England	55.62	80,000	25

Staff resource and skill mix

Delivering efficient and effective mechanical thrombectomy services for ischaemic stroke patients requires a multidisciplinary team consisting of neurointerventionists (or interventionists with expertise in neurology), neuroradiologists and radiographers, consultant stroke physicians skilled in thrombolysis, anaesthetists, and nurses with expertise in radiography and stroke care[5, 21, 28, 41]. Interventionists with neurological expertise or neurointerventionists are key to delivering these services as they have the necessary skills to perform the mechanical thrombectomy procedure. Therefore providing 24/7 access to mechanical thrombectomy is likely to have substantial resource implications for interventionists/neurointerventionists and imaging specialists (including angiography suite staff), with a knock-on effect on diagnostic neuroimaging services[21, 41].

Estimates of the number of clinical staff needed to provide a comprehensive stroke service, including thrombectomy, vary. One study estimated that providing a 24/7 thrombectomy service would require at least five operators capable of performing the procedure and at least 150 thrombectomy procedures per annum to maintain clinical competence for these five individuals[21]. Another report proposed that a hyper-acute stroke unit with 600 new admissions per annum would require an estimated 10.5 medical professionals[41].

Training requirements

The BSNR and the UK Neurointerventional Group published guidance in 2016 on recommended components, content and duration of training for staff participating in mechanical thrombectomy services[42].

Resource requirements

Provision of mechanical thrombectomy services requires access to a range of on-site resources including neurocritical care, neurosurgical support, catheterisation facilities and specialist inpatient and outpatient stroke services[5, 41]. Hospitals offering mechanical thrombectomy also need rapid access to advanced brain imaging facilities, such as CT perfusion, and neuroendovascular experts. British standards for providing mechanical thrombectomy recommend that all hyper-acute stroke units (HASU) have:

- 24-hour availability of, and access to, consultant stroke physicians

- Immediate access to CT angiography, CT perfusion and MRI facilities as required

- Direct admission to the HASU from accident and emergency within one hour of patient arrival

- Capacity for continuous physiological monitoring including electrocardiogram (ECG), oximetry and blood pressure

- Specialist stroke ward rounds seven days per week

- Nurses trained in swallowing screening, stroke neurological assessment, eligibility assessment for thrombolysis and administering thrombolysis

- At least 40–60 thrombectomy procedures per annum to maintain clinical competencies.

Streamlining time to recanalisation

Two studies reported results from quality improvement projects aimed at reducing the time from arrival at hospital to reperfusion by thrombectomy in patients with ischaemic stroke[43, 44]. The first study was a prospective analysis of patients with ischaemic stroke arriving at a tertiary academic hospital between April 2012 and July 2014[43]. The time between each step in the treatment process was documented during an initial 17 month 'pre-optimisation' period and a 12 month 'post-optimisation' phase. Between the two phases a series of changes were introduced to optimise workflow and reduce the time to treatment for patients with ischaemic stroke. Five main sources of delay were identified prior to the quality improvement project: serial rather than parallel workflow; inefficient communication; patient transport; imaging; and lack of consistent feedback. The hospital introduced multiple changes with the aim of reducing these delays:

- Advance notifications from ambulance services were sent to the stroke team as well as the emergency department.

- Early communication between the emergency department and stroke team was prioritised.

- The ambulance service delivered patients directly to the CT scanning facility. Patients who had received prior CT imaging at a referral hospital were taken directly to the CT angiography suite.

- The neurointervention team was activated prior to advanced imaging and patient arrival at the CT angiography suite.

- All non-essential interventions were deferred until after imaging and thrombectomy when possible.

- Point of care laboratory testing was performed in the CT scanner, as was IV thrombolysis.

- Feedback on patient progress was regularly provided to all team members.

In total 286 patients were included in the study; 178 in the pre-optimisation phase and 108 in the post-optimisation period. Following implementation of the changes there were statistically significant improvements in the median time from angiography suite arrival to puncture, CT scan to puncture, puncture to reperfusion, hospital door to puncture and hospital door to reperfusion (table 11). No statistically significant differences were found in functional independence at 90 days (mRS 0-2). This could be a consequence of the study being underpowered to detect differences in clinical outcomes. The authors reported that an unintended consequence of the improvement project was a statistically significant improvement in time from hospital door to thrombolysis which reduced from 56 minutes (IQR 52 to 68 minutes) to 30 minutes (IQR 26 to 48 minutes), p=0.002.

Table 11: median time for each step in the stroke care process pre- and post-optimisation of patient flow at one hospital[43]

Time period	Pre-optimisation Median (IQR)	Post-optimisation Median (IQR)	p value
Symptom onset to hospital arrival (minutes)	202.5 (88 to 350)	240 (135 to 348)	0.17
Door to CT scan (minutes)	14 (6 to 28)	11 (5 to 22)	0.20
CT scan to angiography suite (minutes)	64 (33 to 97)	45 (30 to 75)	0.05
Angiography suite to puncture (minutes)	16 (11 to 21)	10 (9 to 15)	<0.001
CT scan to puncture (minutes)	80 (50 to 118)	57 (40 to 86)	<0.0001
Puncture to reperfusion (minutes)	63 (40 to 92)	47 (31 to 74)	0.0005
Door to puncture (minutes)	105 (67 to 145)	67 (45 to 103)	0.0002
Door to reperfusion (minutes)	334 (258 to 477)	303 (215 to 437)	0.04

The second quality improvement project aimed to reduce hospital door to angiographic reperfusion time to 120 minutes within 12 months by implementing a multi-tiered notification system[44]. This was a prospective study, although data on patients treated prior to introduction of the notification system were gathered retrospectively. Consecutive ischaemic stroke patients who arrived at the emergency department – or were transferred from a referring hospital – between April 2015 and May 2017 were included in the analysis. As with the previous study, the main targets for improvement were inefficiencies in patient triage and interdisciplinary communication. The notification system implemented in this project had three tiers which involved pager alerts to key staff for each stage. The alerts for each tier escalated based on the probability of mechanical thrombectomy being required and triggered involvement of additional specialist staff at each stage. Tier one was initiated based on evaluation of the patient in the emergency department. Tier two prompted advanced imaging using CT angiography and CT perfusion in preparation for thrombectomy. Tier three confirmed mechanical thrombectomy to essential interventional staff. Patients referred from another hospital went directly to tier two, which could be triggered by the referring hospital.

Thirty-four patients were treated with mechanical thrombectomy prior to implementation of the notification system and 28 patients were treated afterwards. The median time from hospital door to reperfusion was significantly shorter following introduction of the notification system: 129 minutes (range 71 to 434 minutes) versus 114.5 minutes (range 64 to 364 minutes), p=0.02. There was no statistically significant difference in median time from symptom onset to reperfusion for the complete patient sample, however time from symptom onset to reperfusion was significantly shorter in the sample of patients admitted directly to the emergency department (median 506 minutes [range 280 to 868 minutes] versus 233 minutes [range 148 to 890 minutes], p=0.02). Patients treated after introduction of the notification system spent significantly less time in the neurocritical care ward: 4 days (range 2 to 21 days) versus 3 days (range 1 to 9 days), p=0.006. No statistically significant differences were found for successful reperfusion rate, inpatient mortality, 90-day mortality, functional independence at 90 days (mRS 0-2) or length of hospital stay.

'Opening hours'

The 2018 report from the Scottish Stroke Improvement Programme calculated the number of confirmed ischaemic stroke patients arriving in hospital by hour of the day and day of the week between 2015 and 2017 (SSIP p39, table 6.2)[6]. Approximately 73% of ischaemic stroke patients in Scotland were admitted to hospital between 07:00 and 19:00, with little variation in the proportion of patients arriving in hospital on a given day of the week.

In an older report from BASP, 95% of ischaemic strokes suitable for mechanical thrombectomy were estimated to occur between 07:00 and 23:00[41]. The authors of the report submit this data as a rationale for gradually extending stroke services, including thrombectomy, towards 24/7 access rather than trying to implement immediate cover for the full 24-hour day.

Imaging

The consensus among authors of papers on mechanical thrombectomy appears to be that diagnostic imaging or advanced brain imaging should occur as quickly as possible after a patient with suspected ischaemic stroke arrives at hospital[15, 21, 41].

One additional study retrospectively evaluated the effect of referral hospital CT perfusion imaging prior to transfer of ischaemic stroke patients to a comprehensive stroke centre for mechanical thrombectomy[45]. The comprehensive stroke centre routinely received patients from eleven referring hospitals, five of which were provided with CT perfusion imaging facilities and RAPID software for interpretation of the resultant images. Between April 2014 and April 2017 thirty-four patients were transferred to the comprehensive stroke centre for mechanical thrombectomy following CT perfusion imaging at the referring hospital; 98 patients were transferred from referral facilities that did not have CT perfusion capabilities. Median time from patient arrival at the comprehensive stroke centre to puncture was significantly shorter for patients transferred following CT perfusion imaging at the referring hospital: median 12 minutes (IQR 8 to 16 minutes) versus 48.5 minutes (IQR 32.8 to 71.8 minutes), p<0.001. There were no statistically significant differences between groups for 'door in door out' time at the referring hospital or functional independence (mRS 0-2).

Scottish Ambulance Service

Rapid transportation of patients with suspected ischaemic stroke to hospital, and if necessary between hospitals, is essential for effective stroke management including mechanical thrombectomy[28]. The UK standards proposed for mechanical thrombectomy services recommend developing pre-hospital algorithms for dispatch of emergency services, assessment of patients, pre-notification of destination hospitals and transport strategies (see models of service delivery)[41].

In Scotland the Scottish Ambulance Service have already committed to improving outcomes for stroke patients[46]. To date the Scottish Ambulance Service has worked on improving patient triage and deploying appropriately skilled staff to ensure hyper-acute stroke patients receive definitive care within 60 minutes. They have also been engaging with regional Stroke Managed Care Networks to streamline and improve access to specialist stroke care. The national move towards development of specialist centres for specific clinical conditions, including stroke, that affect traditional board boundaries and patient flow is seen as one of the key drivers for future ambulance service planning.

Currently the Scottish Ambulance Service operates in five regional divisions from three ambulance control centres[46]. In addition to a fleet of road ambulances, the service has two fixed-wing aircraft and two helicopters operating from Glasgow, Inverness and Aberdeen. An additional helicopter is provided by the Scottish Charity Air Ambulance. In 2016–2017 the Scottish Ambulance Service conveyed 11,642 patients with suspected stroke to hospital[7].

Conclusion

Based on robust evidence from meta-analyses of RCTs, mechanical thrombectomy with/without IV thrombolysis results in an increased likelihood of patients regaining functional independence within

three months of an ischaemic stroke due to large vessel occlusion compared with standard medical care alone. Data from recent RCTs included in a meta-analysis indicate the beneficial effect of mechanical thrombectomy on post-stroke functional independence continues in ischaemic stroke patients treated more than six hours after symptom onset (median time to treatment 10.8 hours). The beneficial effects on patients' functional outcomes appears to be achievable without a significant increase in 90-day mortality or symptomatic intracranial haemorrhage risk.

UK-based evidence suggests that stent retriever mechanical thrombectomy is likely to be cost effective compared with standard medical care for the treatment of ischaemic stroke due to large vessel occlusion.

Introducing mechanical thrombectomy services has implications for NHSScotland including costs, staff resource and training needs, facility requirements (particularly advanced neuroimaging), ambulance services, general infrastructure and logistics. A statistically significant negative association between mechanical thrombectomy procedure volume and patient mortality rate suggests that mechanical thrombectomy should be limited to a small number of hospitals with access to advanced imaging and clinical expertise. Secondary evidence based mainly on retrospective observational studies indicates the mothership model of thrombectomy service organisation is associated with more patients achieving functional independence at 90 days compared with the drip and ship model of care. However the choice of service delivery model should include consideration of additional contextual factors such as geography, travel time/distance between hospitals, availability of experienced staff, the urban-rural split, and volume of ischaemic stroke patient admissions per annum.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

Acknowledgements

References

1. Stroke Association. State of the nation: stroke statistics. 2018 [cited 2018 Oct 11]; Available from: https://www.stroke.org.uk/system/files/sotn_2018.pdf.

2. World Health Organization. Stroke, cerebrovascular accident. [cited 2018 Oct 11]; Available from: http://www.who.int/topics/cerebrovascular_accident/en/.

3. Scottish Intercollegiate Guidelines Network. Management of patients with stroke or TIA: assessment, investigation, immediate management and secondary prevention. 2008 [cited 2018]; Available from: https://www.sign.ac.uk/assets/sign108.pdf.

4. EUnetHTA. Endovascular therapy using mechanical thrombectomy devices for acute ischaemic stroke. 2016 [cited 2018 Oct 11]; Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Mechanical-thrombectomy-devices-for-acute-ischaemic-stroke_Rapid-REA_Updated-and-Final-Feb-2016.pdf.

5. Evans MRB, White P, Cowley P, Werring DJ. Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. Pract Neurol. 2017;17(4):252-65.

6. NHS National Services Scotland. Scottish stroke improvement programme. 2018 [cited 2018 Nov 22]; Available from: https://www.strokeaudit.scot.nhs.uk/Publications/docs/2018-07-10-SSCA-Report.pdf.

7. ISD Scotland. Scottish stroke statistics: year ending 31 March 2017. 2018 [cited 2018 Oct 11]; Available from: https://www.isdscotland.org/Health-Topics/Stroke/Publications/2018-01-30/2018-01-30-Stroke-Report.pdf.

8. Scottish Government. The Scottish health survey: 2017 edition - volume 1 - main report. 2018 [cited 2018 Oct 11]; Available from: https://www.gov.scot/Resource/0054/00540654.pdf.

9. National Institute for Health and Care Excellence (NICE). Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (update). 2018 [cited 2018 Nov 26]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ng10071/consultation/html-content-2.

10. Scottish Health Technologies Group. What is the clinical effectiveness, safety and cost effectiveness of endovascular therapy using mechanical thrombectomy devices for patients with acute ischaemic stroke? 2016 [cited 2018 Oct 30]; Available from: http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/shtg_-_evidence_notes/evidence_note_61.aspx.

11. Flynn D, Francis R, Halvorsrud K, Gonzalo-Almorox E, Craig D, Robalino S, *et al.* Intra-arterial mechanical thrombectomy stent retrievers and aspiration devices in the treatment of acute ischaemic stroke: a systematic review and meta-analysis with trial sequential analysis. Eur Stroke J. 2017;2(4):308-18.

12. Vidale S, Agostoni E. Endovascular treatment of ischemic stroke: an updated meta-analysis of efficacy and safety. Vasc Endovasc Surg. 2017;51(4):215-9.

13. Barral M, Boudour S, Viprey M, Giroudon C, Aulagner G, Schott AM, *et al.* Stent retriever thrombectomy for acute ischemic stroke: a systematic review and meta-analysis of randomized controlled trials, including THRACE. Rev Neurol. 2018;174(5):319-26.

14. Vidale S, Longoni M, Valvassori L, Agostoni E. Mechanical thrombectomy in strokes with large-vessel occlusion beyond 6 hours: a pooled analysis of randomized trials. J Clin Neurol. 2018;14(3):407-12.

15. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CBL, Dippel DW, *et al.* Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. JAMA. 2016;316(12):1279-88.

16. Saber H, Rajah GB, Kherallah RY, Jadhav AP, Narayanan S. Comparison of the efficacy and safety of thrombectomy devices in acute stroke: a network meta-analysis of randomized trials. J Neuroint Surg. 2018;10(8):729-34.

17. Boudour S, Barral M, Gory B, Giroudon C, Aulagner G, Schott A-M, *et al.* A systematic review of economic evaluations on stent-retriever thrombectomy for acute ischemic stroke. J Neurol. 2018;265(7):1511-20.

18. Lobotesis K, Veltkamp R, Carpenter IH, Claxton LM, Saver JL, Hodgson R. Cost-effectiveness of stent-retriever thrombectomy in combination with IV t-PA compared with IV t-PA alone for acute ischemic stroke in the UK. J Med Econ. 2016;19(8):785-94.

19. Ganesalingam J, Pizzo E, Morris S, Sunderland T, Ames D, Lobotesis K. Cost-utility analysis of mechanical thrombectomy using stent retrievers in acute ischemic stroke. Stroke. 2015;46(9):2591-8.

20. Ismail M, Armoiry X, Tau N, Zhu F, Sadeh-Gonik U, Poitin M, *et al.* Mothership versus drip and ship for thrombectomy in patients who had an acute stroke: a systematic review and meta-analysis. J Neurointerv Surg. 2018 [In Press].

21. Allen M, Pearn K, James M, Ford GA, White P, Rudd AG, *et al.* Maximising access to thrombectomy services for stroke in England: a modelling study. Eur Stroke J. 2018 [In Press].

22. Holodinsky JK, Patel AB, Thornton J, Kamal N, Jewett LR, Kelly PJ, *et al.* Drip and ship versus direct to endovascular thrombectomy: the impact of treatment times on transport decision-making. Eur Stroke J. 2018;3(2):126-35.

23. Brekenfeld C, Goebell E, Schmidt H, Henningsen H, Kraemer C, Tebben J, *et al.* 'Drip-and-drive': shipping the neurointerventionalist to provide mechanical thrombectomy in primary stroke centers. J Neurointerv Surg. 2018;10(10):932-6.

24. Wei D, Oxley TJ, Nistal DA, Mascitelli JR, Wilson N, Stein L, *et al.* Mobile interventional stroke teams lead to faster treatment times for thrombectomy in large vessel occlusion. Stroke. 2017;48(12):3295-300.

25. Halvorsrud K, Flynn D, Ford GA, McMeekin P, Bhalla A, Balami J, *et al.* A Delphi study and ranking exercise to support commissioning services: future delivery of thrombectomy services in England. BMC Health Serv Res. 2018;18(1):135.

26. NHS England. Clinical commissioning policy: mechanical thrombectomy for acute ischaemic stroke (all ages). 2018 [cited 2018 Sept 10]; Available from: https://www.england.nhs.uk/wp-content/uploads/2018/03/d04-mechanical-thrombectomy-for-acute-ischaemic-stroke-v2.pdf.

27. Sentinel Stroke National Audit Programme. Rising to the challenge: the fourth SSNAP annual report. Stroke care received between April 2016 to March 2017. 2017 [cited 2018 Nov 22]; Available from: https://www.strokeaudit.org/Documents/AnnualReport/2016-17-SSNAP-Annual-Report.aspx.

28. Health Information and Quality Authority. Health technology assessment of a national emergency endovascular service for mechanical thrombectomy in the managemnt of acute ischaemic stroke. 2017 [cited 2018 Sept 10]; Available from: https://www.hiqa.ie/sites/default/files/2017-02/Mechanical-Thrombectomy-technical-report.pdf.

29. Frønsdal KB, Skår Å, Stoinska-Schneider A, Ormstad SS, Fure B. Mechanical thrombectomy for acute ischaemic stroke: executive summary. 2016 [cited 2018 Nov 22]; Available from: https://www.fhi.no/en/publ/2016/mekanisk-trombektomi-ved-akutt-hjerneinfarkt/.

30. Frønsdal KB. Mechanical thrombectomy for treating acute ischemic stroke. HTAi conference; June 2018; Vancouver.

31. Ludwig Boltzmann Institut. Organisational aspects of thrombectomy in Austria. HTAi conference; June 2018; Vancouver.

32. Ferrari J, Tomek A, Polák M, Santalucia P. Experience from today for the stroke care of the future. 2018 [cited 2018 Nov 22]; Available from: http://www.oruen.com/wp-content/uploads/2018/08/Angels-article-new.pdf.

33. Haute Autorité de Santé. How to assess and present organisational impact in HTAs? HTAi conference; June 2018; Vancouver.

34. University of Calgary. Endovascular therapy (mechanical thrombectomy) for ischemic stroke: a health technology assessment and implementation analysis. 2016 [cited 2018 Nov 22]; Available from: https://www2.gov.bc.ca/assets/gov/government/ministries-organizations/ministries/health/evt-hta-final.pdf.

35. Rinaldo L, Brinjikji W, Rabinstein AA. Transfer to high-volume centers associated with reduced mortality after endovascular treatment of acute stroke. Stroke. 2017;48(5):1316-21.

36. Sheth SA, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, et al. Rapid learning curve for Solitaire FR stent retriever therapy: evidence from roll-in and randomised patients in the SWIFT trial. J Neurointerv Surg. 2016;8(4):347-52.

37. Beumer D, van Boxtel TH, Schipperen S, van Zwam WH, Lycklama A Nijeholt GJ, Brouwer PA, et al. The relationship between interventionists' experience and clinical and radiological outcome in intra-arterial treatment for acute ischemic stroke. A MR CLEAN pretrial survey. J Neurol Sci. 2017;377:97-101.

38. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46-110.

39. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: consensus statement by ESO-Karolinska Stroke Update 2014/15, supported by ESO, ESMINT, ESNR and EAN. Int J Stroke. 2016;11(1):134-47.

40. McMeekin P, White P, James MA, Price CI, Flynn D, Ford GA. Estimating the number of UK stroke patients eligible for endovascular thrombectomy. Eur Stroke J. 2017;2(4):319-26.

41. White PM, Bhalla A, Dinsmore J, James M, McConachie N, Roffe C, et al. Standards for providing safe acute ischaemic stroke thrombectomy services. 2015 [cited 2018 Sept 10];

Available from: https://basp.ac.uk/wp-content/uploads/2016/12/Final_ThrombectomyStandardsSeptember-2015-2-1-1.pdf.

42. Lenthall R, McConachie N, White P, Clifton A, Rowland-Hill C. BSNR training guidance for mechanical thrombectomy. 2016 [cited 2018 Nov 02]; Available from: http://bsnr.org.uk/wp-content/uploads/2016/06/BSNR-training-response-to-MT-evidence-FINAL-23.1.16.pdf.

43. Aghaebrahim A, Streib C, Rangaraju S, Kenmuir CL, Giurgiutiu DV, Horev A, *et al.* Streamlining door to recanalization processes in endovascular stroke therapy. J Neurointerv Surg. 2017;9(4):340-5.

44. Goldstein ED, Schnusenberg L, Mooney L, Raper CC, McDaniel S, Thorpe DA, *et al.* Reducing door-to-reperfusion time for mechanical thrombectomy with a multitiered notification system for acute ischemic stroke. Mayo Clin Proc Innov Qual Outcomes. 2018;2(2):119-28.

45. Aghaebrahim A, Sauvageau E, Aguilar-Salinas P, Cortez G, Santos R, Hanel RA. Referral facility CT perfusion prior to inter-facility transfer in patients undergoing mechanical thrombectomy. J Neurointerv Surg. 2018;10(9):818-22.

46. Scottish Ambulance Service. Towards 2020: taking care to the patient. 2016 [cited 2018 Nov 02]; Available from: http://www.scottishambulance.com/UserFiles/file/TheService/Publications/Strategic%20Plan_Online%20pdf.pdf.

Appendix 1: abbreviations

ASPECTS	Alberta Stroke Programme Early CT Score
BASP	British Association of Stroke Physicians
BSNR	British Society of Neuroradiologists
CHEERS	consolidated health economic evaluation reporting standards
CI/CrI	confidence interval/credible interval
CT	computed tomography
CTA	computed tomography angiography
DSA	digital subtraction angiography
ECG	electrocardiogram
GRADE	grading of recommendations assessment, development and evaluation
HASU	hyper-acute stroke unit
HIQA	Health Information and Quality Authority
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
ICH	intracranial haemorrhage
IPD	individual patient data
IQR	inter-quartile range
IV	intravenous
MCA	middle cerebral artery
MR	magnetic resonance
MRA	magnetic resonance angiography
mRS	modified Rankin Scale
NICE	National Institute for Health and Care Excellence
NIHSS	National Institute of Health Stroke Scale
NMA	network meta-analysis
OR	odds ratio
QALY	quality adjusted life year
RCT	randomised controlled trial
RR	relative risk

rt-PA	recombinant tissue plasminogen activator
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
TIA	transient ischaemic attack